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Robertsonian (15q;15q) Translocation in a Child With Angelman Syndrome: Evidence of Uniparental Disomy

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A balanced Robertsonian translocation 45,XY,t(15q15q) was detected in a patient with mental retardation, microcephaly, and hypertonia. Deletion of the 15q11q13 region was unlikely based on fluorescence in situ hybridization studies that revealed hybridization of appropriate DNA probes to both arms of the Robertsonian chromosome. Inheritance of alleles from 13 highly polymorphic DNA markers on chromosome 15 showed paternal uniparental isodisomy. The clinical, cytogenetic, and molecular results are consistent with a diagnosis of Angelman syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: chromosome 15 translocations, Robertsonian translocation 15q15q, Angelman syndrome, Prader-Willi syndrome, paternal uniparental disomy

INTRODUCTION

Interstitial deletion of 15q11-q13 is seen in the Angelman (AS) and Prader-Willi (PWS) syndromes. Molecular studies have shown the most common deletion region to be identical in both AS and PWS [Kuwano et al., 1992; Christian et al., 1995]. For cases without deletion, maternal uniparental disomy explains ~20% of PWS but only ~5% of AS [Malcolm et al 1991; Ledbetter et al., 1992]. One mechanism for uniparental disomy would be inheritance of Robertsonian translocation 15q15q as described in several cases of PWS but only one previously reported case of AS [Freeman et al. 1993]. Here we report a second case of apparently balanced t(15q15q) with paternal uniparental disomy in a patient with clinical findings that are typical of the Angelman syndrome.

CLINICAL REPORT

The propositus (Fig. 1) was evaluated at age 2½ years because of developmental delay and microcephaly. He weighed 2.8 kg (40th centile) after a term gestation complicated by ulcerative colitis; increased in utero activity was noted in comparison to a prior pregnancy. Aside from a paternal brother who died at age 13 from renal disease, family history was normal. The father was age 31 years and the mother age 29 years at conception. Early medical problems included "colicky" behavior with reflux for the first 2 months, abnormal sleep patterns with frequent nocturnal awakening for the first year, and eczema, moniliasis, otitis, and bronchitis during the first 2 years. Delayed development was noted at age 6 months with walking at age 2 years and little progress in speech despite normal audiology screening. Physical examination at age 2½ years showed a height of 86 cm (< 3rd centile for age; 50th centile for age 22 months), a weight of 11.6 kg (6th centile for age), and a head circumference of 46.5 cm (< 3rd centile for age; 50th centile for age 10 months). The face appeared normal with a small jaw, normal palate and ears, and normal dermatoglyphics and genitalia. He had hypertonia of the heel cords and wrists with increased reflexes and bilateral presence of the Babinski sign. At age 6 years he is described by his parents as hyperactive and distractible with self-injuring behavior and communication by gestures.

RESULTS AND DISCUSSION

Chromosome studies on the propositus were performed by standard techniques and revealed an abnormal 45,XY,t(15q15q) karyotype in each of twenty prometaphase cells analyzed (Fig. 2). Parental chromosome studies were normal. Fluorescent in situ hybridization (FISH) was performed on metaphase chromosomes from the patient using cosmid probes corresponding to D15S11

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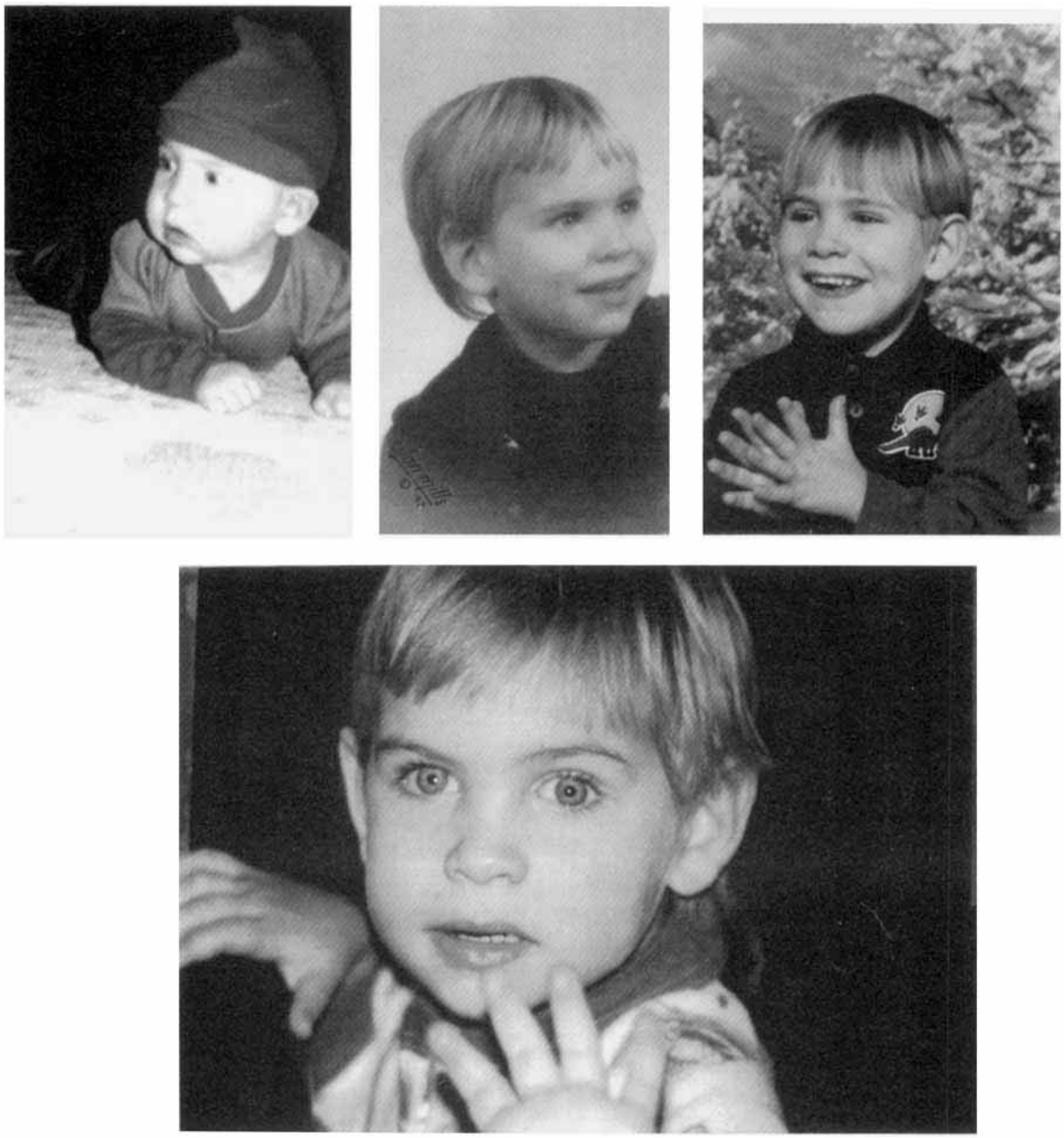

Fig. 1. The propositus at ages 6 months (upper left), 2½ years (bottom), 4 years (middle), and 6 years (upper right).

and GABRB3 from the PWS/AS critical region (15q11-q13) by methods previously described [Kuwano et al., 1992]. Both probes demonstrated two signals on the translocation chromosome, ruling out a deletion of the Angelman critical region (data not shown).

DNA was prepared from the patient and both parents using standard techniques. Highly polymorphic microsatellite markers from chromosome 15 were selected to determine the parental origin of the t(15;15) [Beckmann et al., 1993; Mutirangura et al., 1993; Christian et al., 1995]. The microsatellite PCR analysis was performed as described using 40 ng of genomic DNA per reaction [Christian et al., 1995]. All 13 markers showed the presence of a single allele that matched one allele of the father. Seven markers (S541/S542, S11, GABRB3, 155CA-2, S125, and S131; listed in order with centromere-telomere orientation) were fully informative for the absence of a maternal allele, indicating paternal uniparental isodisomy (Fig. 3).

The propositus has several characteristics of Angelman syndrome including severe speech and developmental delay, microcephaly, hypertonia, hand flapping, and strabismus. The cytogenetic and molecular evidence for paternal uniparental disomy 15, taken together

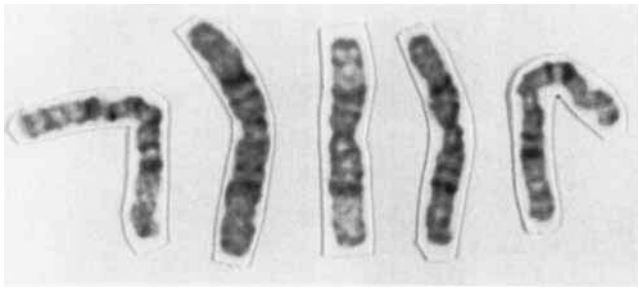

Fig. 2. Partial karyotype showing the Geimsa-banded t(15;15) chromosome from five separate prometaphase spreads.

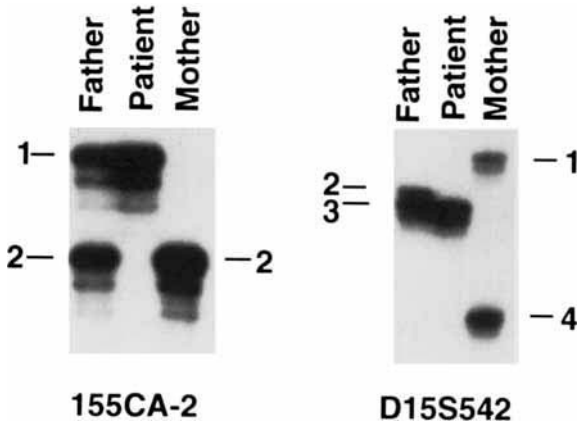

Fig. 3. Microsatellite analysis using polymorphic markers from chromosome 15. Marker 155CA-2 (**left panel**) shows the father to be heterozygous 1,2, the mother to be homozygous 2,2, and the patient to be homozygous 1,1. Marker D15S542 (**right panel**) shows the father to be heterozygous 2,3, the mother to be heterozygous 1,4, and the patient to be homozygous 3,3. For both markers the patient demonstrates the presence of one paternal allele consistent with paternal isodisomy.

with the suggestive phenotype, are best explained by a diagnosis of Angelman syndrome. Because the propositus lacks a typical facial appearance and gelastic seizures, he may represent the milder phenotype of Angelman syndrome described in patients with uniparental disomy [Bottani et al., 1994].

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